Experiment and Theory in Multicomponent Reaction Development

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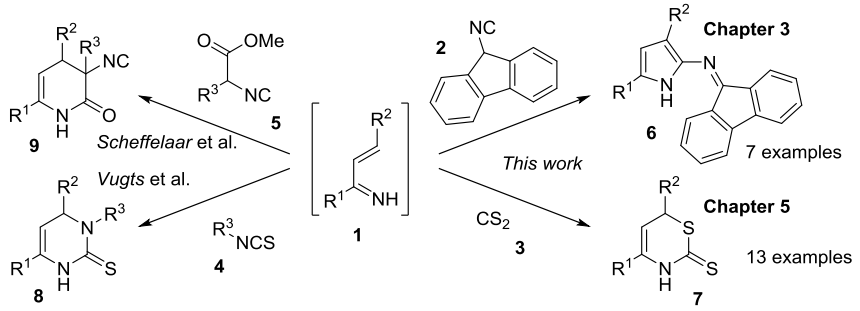
Summary

The chemistry described in this thesis is a further exploration of multicomponent chemistry involving two reactive intermediates, namely imines and 1-azadienes. Known modular reaction sequences (MRS) involving these intermediates were expanded using single reactant replacement (SRR), arriving at novel multicomponent reactions of which also some follow up chemistry was explored. In this research, computational tools were developed to not only explain and predict the results observed experimentally, but also to steer the research thus optimizing experimental efforts.

First, we set out to expand the already rich chemistry of 1-azadienes. These reactive intermediates are formed *via* a Horner-Wadsworth-Emmons (HWE) reaction after which reaction partners can be added (**Scheme 1**). An overview of this chemistry is presented in **Chapter 1**, along with key concepts used further on in this thesis. Additionally, in **Chapter 2** an extensive overview on isocyanide additions on conjugate systems in ring forming MCRs is discussed with the goal to explore known chemistry in this field.

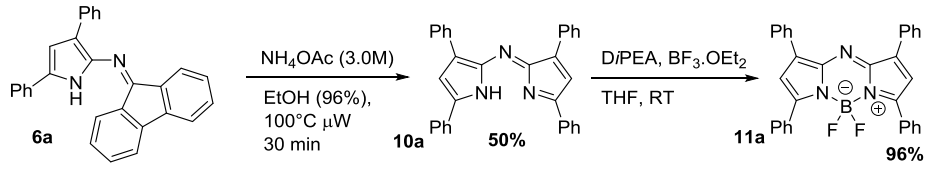


Scheme 1. Known reactions of 1-azadienes (left) and novel reactions as described herein (right).

As described in **Chapter 3** and by using an SRR-approach, α-acidic isocyanides **5** were replaced with α-acidic 9*H*-fluorenyl isocyanide (**2**) in the reaction with 1-azadienes. This isocyanide carbon is able to add to the 1-azadiene in a formal [4+1] reaction, leading to fluorenylidenimino pyrroles **6**. We reason 9*H*-fluorenyl isocyanide activates the 1-azadiene without thereby also activating its α-carbon as a nucleophile, explaining this difference in reactivity between the two species of isocyanide. Furthermore, TDDFT calculations were performed to explain the deep color of these molecules.

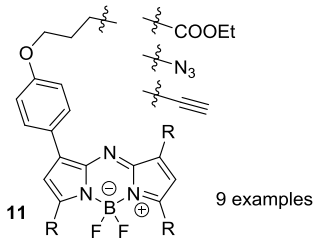
Alternatively, and as described in **Chapter 5**, we replaced isothiocyanates **4** in its reaction with 1-azadienes by carbon disulfide, furnishing thiazine-2-thiones **7**. Alternatively, in the analogous coupling with carbon dioxide no reaction was observed, which could be rationalized using DFT calculations.

In addition to both novel MCRs, *in-situ* follow up chemistry was explored in **Chapter 4** and **Chapter 6**. Firstly, a bright blue coloured side product was found in the optimization towards pyrrole **6**. After isolation, identification and a short review on the reaction conditions, dipyrrole **10a** could be isolated in 50% yield and the subsequent borylation proved to be near quantatative. This gave us an efficient and modular route towards the already widely employed *aza*-BODIPY scaffold (**11**) opening up the possibility for more tailored fluorescent chemical probes.



Scheme 2. Synthesis of tertaphenyl *aza*-BODIPY 11a.

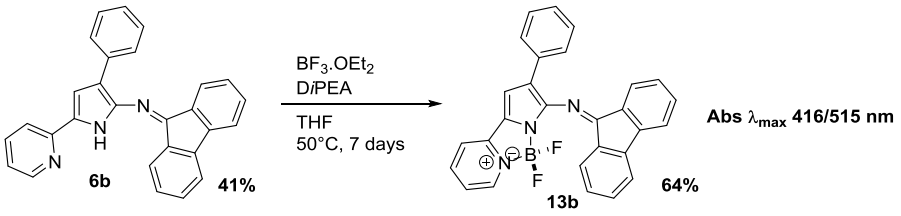
After this, a small library of heterodimeric and linkable aza-BODIPYs was synthesized, which are now in the process of being screened in a biochemical setting as fluorescent labels (**Scheme 3**).



Scheme 3. Heterodimeric and linkable library of *aza*-BODIPYs 11.

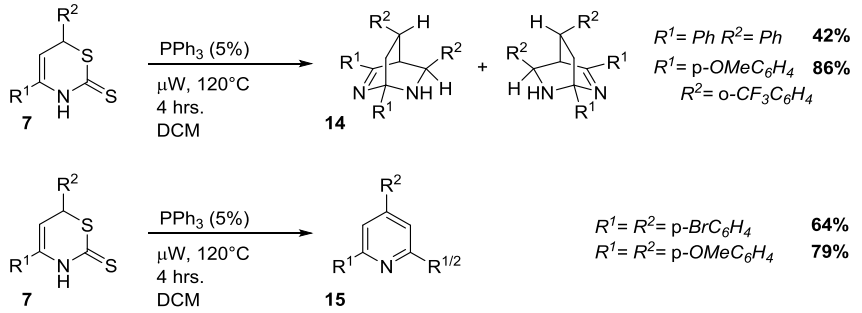
Next to the straightforward *aza*-BODIPY synthesis, we envisioned an even more direct route towards BOPYPY fluorophores in which a pyridyl nitrogen acts as the second chelating atom (**Scheme 8**). Unfortunately, BOPYPY **13b** fails to emit light. We hypothesize this is either due to thermal relaxation of this more

dynamic system or to the absorption of the fluorescence (from the HOMO-1 to LUMO excitation) by the HOMO to LUMO absorption. Backed by DFT calculations we chose not to investigate this system any further.



Scheme 4. Synthesis of 13b.

In **Chapter 6** we report on the unexpected formation of a 1-azadiene dimer from thiazine-2-thiones under prolonged microwave irradiation (**Scheme 11**). We compare this dimerization with earlier approaches to these interesting molecules and elaborate on the observed diastereo- and chemoselectivity.



Scheme 5. Synthesis of 14 and 15 by microwave irradiation of thiazine 7.

Having used computational chemistry in an explanatory fashion throughout this thesis, we finally set out to explore an efficient and pragmatic methodology that truly integrates computational and experimental organic chemistry tools in an iterative fashion to drive multicomponent reaction exploration (**Figure 1**).

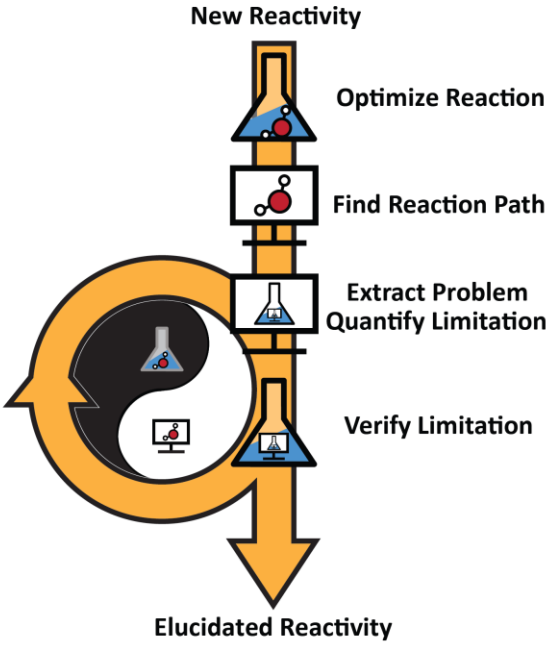
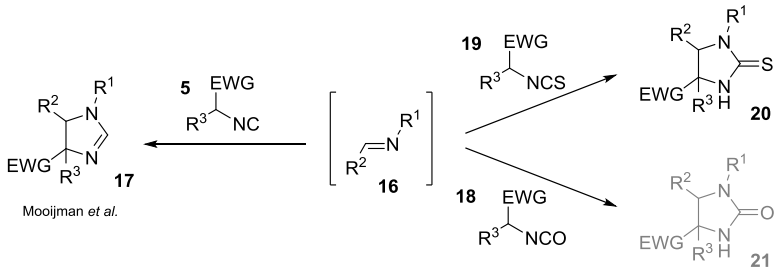


Figure 1. Our integrative methodology for iterative theory-experiment driven multicomponent reaction exploration.

To demonstrate our integrative theory-experiment driven approach for reaction development we focus here on the MCR between imines **16** and isothiocyanates **19** affording imidazolin-2-(thi)ones **20**, as described by us earlier (**Scheme 6**).



Scheme 6. Reactivity of imines and α-isocyanoacetates (left) and iso(thio)cyanates (right).

The clarification of the reaction profile of a model system led to the extraction of a limiting parameter, *i.e.* the difference in proton affinity (ΔPA) between the imine and the iso(thio)cyanate. Differences between the theoretical and

experimental trends then led to refinement of the reaction profile (C-C bond formation as a second decisive parameter). Furthermore, the combined experimental and computational results from **Chapter 7** and **8** show that not only the electronics of the C-C bond formation but also the sterics are important to predict the reaction outcome.

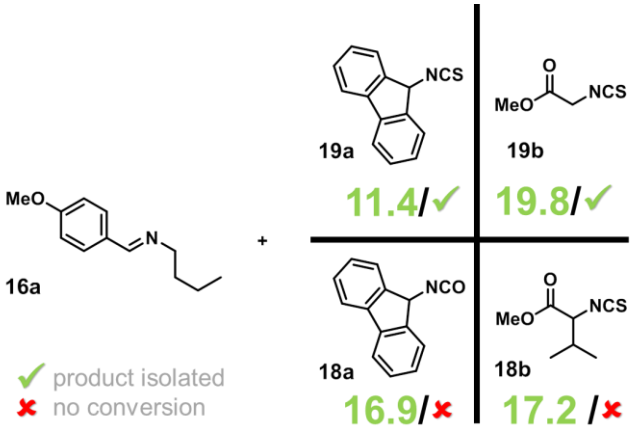


Table 1. Selected examples (in DCM) from Chapter 7 and Chapter 8 showcasing both electronic and steric influences on the C-C bond formation.

As a final remark, we strongly feel this iterative methodology is an important step towards better integration of the two fields and will help to streamline efforts in the future.